Guidance for reporting clinical trial registry records and published protocols use in systematic reviews of interventions

Julia Bidonde (julia.bidonde@fhi.no)
Norwegian Institute of Public Health Division of Health Services https://orcid.org/0000-0001-7535-678X

Jose Francisco Meneses-Echavez
Folkehelseinstituttet

Angela Jean Busch
University of Saskatchewan College of Medicine

Catherine Boden
University of Saskatchewan

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Abstract

Background: Transparency is a tenet of systematic reviews. Searching for clinical trial registry records and published protocols has become a mandatory standard when conducting a systematic review of interventions. However, there is no comprehensive guidance for review authors on how to report the use of registry records and published protocols in their systematic review. The objective of this study was to generate initial guidance to assist authors of systematic reviews of interventions in the reporting of registry records and published protocols in systematic reviews of interventions. Methods: We used a compilation of the procedures recommended by expert organizations (e.g., Cochrane Collaboration) related to the reporting of use of registry records and published protocols in the conduct of systematic reviews. The compilation was developed by one of the authors in this study and served as a starting point in developing the algorithm. We extracted current practice data related to registry records and published protocols from a stratified random sample of Cochrane systematic reviews of interventions published between 2015 and 2016 (n=169). We identified examples that adhered to or extended the current guidance. Based on the on the elements above, we created the algorithm to bridge gaps and improve current reporting practices. Results: Trial protocols should be used to account for all evidence in a subject area, evaluate reporting bias (i.e. selective reporting and publication bias), and determine the nature and number of ongoing or unpublished studies for planning review updates. Review authors' terminology (e.g., ongoing, terminated) and consequent reporting in the review should reflect the phase of the trial found. Protocols should be clearly and consistently reported throughout the review (e.g. abstract, methods, results) as is done with published articles. Conclusions: Our study expands on available guidance to describe in greater detail the reporting of registry records and published protocols for review authors. We believe this is a timely investigation that will increase transparency in the reporting of trial records in systematic reviews of interventions and bring clarification to current fuzziness in terminology. We invite researchers to provide feedback on our work for its improvement and dissemination. Trial Registration: not applicable

Background

Evidence derived from systematic reviews of interventions plays a vital role in patient care and decision-making [1]. Studies utilizing a randomized design are often preferred, as these provide the most rigorous research design for assessment of the effects of interventions [2]. Health care and policy decision-making require high quality reviews, so it is important to be able to detect potential biases in the included studies. To increase trust in randomized control trials (RCTs), the international scientific community have called for transparency in trial reporting and conduct, and implemented a number of requirements to help this purpose [3]. Prospective trial registration is a cornerstone of transparency and reduction of bias; it is also a way to prevent duplication of research, and informing patients and public of clinical trials they may want to enroll or follow [4].

A trial protocol is a public record that states the question and planned methods of a study. This record helps anyone evaluating (published) results to judge how far it fulfils its original objectives, or if authors

have followed pre-stated methods, or amendments/modifications were needed and why. Systematic review authors can use protocols for several purposes including: a) accounting for all evidence in the subject area (i.e., published and unpublished trials), b) reducing the potential for reporting biases (i.e. publication biases and selective outcome reporting), d) detrmining when updates are needed, which is for example highly relevant in the context of Living Systematic Reviews [5], and e) detecting and evaluating trials that have been terminated. We have presented potential uses of trial registry records (TRR) and published protocols (PP) in Appendix A.

Authors can share their trial protocols in several ways. First, by registering the study in trial registries (e.g., ClinicalTrials.gov). This constitutes the main public source of basic trial registry records information [3]. Second, publishing protocols in peer review journals; this has gained popularity in the recent years. Finally, some (free) web portals (i.e., open science) offer an opportunity for researchers to register their protocol while concurrently receiving feedback from peers. TRR and PP exist independently or in addition to each other creating a reporting challenge for systematic reviewers. While there have been many advances in trial registration and publication, the reporting of TRR/PP within systematic reviews is variable and scattered.

This team conducted a systematic search of the written guidance related to TRR/PP provided by the major systematic review bodies [6] and we identified significant gaps in guidance. Although there is encouragement and increased awareness of the use of protocols in the detections of biases, there is no comprehensive guidance on reporting of TRR/PP use in systematic reviews of interventions. Collectively, the main systematic review bodies have provided some methodological and some conceptual guidance for certain areas of the review process. However, we believe there is a need for greater guidance on the utilization and reporting of TRR/PP.

Methods

The purpose of this study was to expand on available guidance to assist authors of systematic reviews of interventions in the reporting of TRR/PP. The methodological appropriateness of using the TRR/PP in systematic reviews (i.e. comparing the methods and results section within a publication) or questions concerned with use of registries information accuracy (i.e. information on the registry vs published publication) were outside the scope of this study.

Three main sources form the basis of this study:

i. Available methodological guidance by review bodies on TRR/PP identified in Boden et al [6],

ii. Data extracted from a random sample of Cochrane systematic reviews of interventions provided the starting point that helped us identify how review authors were reporting TRR/PP use, and

iii. Our expertise in the critical analysis and discussions in order to highlight potential challenges and areas of integration of all sources. The team has international and collective expertise as Cochrane

reviewers, and in areas of evidence synthesis, information science, and research methods.

i. Available methodological guidance by review bodies

We identified gaps and current guidance on the reporting of TRR/PP in a previous study [6] and we extended this information with the data extracted from Cochrane systematic reviews to provide examples of the guidance and fill gaps where possible. Major organizations producing systematic review recommend reviewers should: search trial registries and electronic databases for TRR/PP, either for new or update reviews; list all sources used; report the search terms used in addition to the bibliographic databases; compare outcomes reported in the 'protocol' and the published report; and request a copy of the study protocol from authors.

ii.Sample of Cochrane systematic reviews of interventions

We evaluated a sample of Cochrane systematic reviews of interventions (hereafter systematic reviews) to ascertain how review authors reported TRR/PP in their reviews. An information specialist (CB) searched the Cochrane Library for one-year period (2015-2016) for systematic reviews. We used the terms "controlled trial*", "rct*", "clinical trial*" and "random*" combined with the Boolean operator "OR". A statistician (DT) selected a random sample with equal group size, stratified by Cochrane Editorial group for a representative sample. Systematic reviews were included if they were: a) a published new or updated review, b) identified as a systematic review (i.e., not a title registration or protocol) of the effectiveness of an intervention, and c) had at least one included randomized controlled trial. We excluded systematic review protocols, network meta-analyses, overviews of reviews, systematic reviews of non-randomized trials, diagnostic, prognostic or methods reviews, and withdrawn systematic reviews. A pair of authors independently screened title and abstract records for inclusion using a software tool [7]; we sample with replacement until we reached approximately 20% of the reviews found by the search. We made decisions following an a priori criteria and consensus meeting with a third author available to resolve disagreements. Authors completed data extraction (JB, CB, JFME) using piloted standardized Excel sheets created for this project. The Cochrane systematic review mandatory sections (i.e., abstract, plain language summary, methods) served as a guide for our data extraction. The team agreed on terms and phrases associated with TRR/PP for example 'protocol,' 'trial registry,' 'NCT' (to identify clinicaltrials.gov registry records), 'ongoing' or 'registry record' to identify sentences or paragraphs reporting TRR/PP. Once we found sections containing these words, we confirmed they referred to TRR/PP and extracted the verbatim excerpt. We used excerpts from the reviews to illustrate our findings.

iii.Development of guidance algorithm

Collectively, the authors have considerable experience in evidence synthesis, and we have held diverse roles in areas including literature searches, clinical research and research methods. To inform this analysis, we engaged in critical reflections on the ways Cochrane authors reported TRR/PP. We used critical analysis of data extracted from the Cochrane reviews and available methodological guidance in our discussions in order to highlight challenges and areas of commonality across sources and to develop

the reporting algorithm. We used direct excerpts from the systematic reviews (when available) to illustrate findings and guide authors in reporting TRR/PP.
Box 1 presents a glossary of terms used in this article to clarify TRR/PP terminology.

Results

Sample of Cochrane reviews

The search yielded 980 citations; after several iterations (exclusion and replacement), we included 169 reviews from 49 Cochrane Review Groups. Forty-seven percent were new reviews were 89% were review updates. Exclusions were due to review type (i.e. network meta-analysis, diagnostic review, protocol), status (i.e. withdrawn review), or content (i.e. no RCT included or empty reviews). We found information about TRR/PP in most sections of the reviews; however, for practical reasons we focused on abstract, methods, results and discussion with associated references, tables and figures.

As with Boden et al [6] who found problems with terminology, our data extraction also indicated inconsistencies in terminology in reporting. Authors used a combination of publication types (protocol, trial registry record), trial statuses (ongoing, completed, terminated) and publication statuses (unpublished, published). Terminology for a particular protocol might be different in one section of the review from another. Further, authors did not consistently cite protocols, in the text and/or the references, making it challenging for readers to access the protocol themselves or track the progress of a protocol through the review. Our results showed authors used terminology suggested by the current guidance, for example "*Searching trial registers can identify unpublished or ongoing trials.*" (Cochrane Handbook, CRD) while in other instances authors expanded it (e.g. ongoing, completed or terminated*).* We recommend that authors refer to the publication type and trial status in the Search Results and PRISMA, and the trial status and publication status as appropriate in later stages of the review. Authors should provide a citation for protocols as they would for any other document type

The following excerpts illustrate the above findings:

a) [Search] *We searched for* ***ongoing or completed unpublished*** *trials in the clinical trial registries…" [8]*

b) [Search] *We searched international trial registries via the World Health Organization trials portal (ICTRP) and ClinicalTrials.gov to identify* ***unpublished and ongoing*** *studies" [9]*

c) [Result] *the database searched identify 5863 records, while the searches for trial registries identified nine records of* ***ongoing, completed or terminated*** *studies…" [10]*

Authors' terminology varied in different parts of the review: they referred to a specific type/status of TRR in the methods section (i.e. searching for ongoing trials) but use a broader term in the results/conclusion sections (i.e. there were no protocols). While this is technically correct, we argue consistency and

specificity in terminology within sections of the review will help with transparency. The following excerpts serve as an illustration:

d) Baker 2016 [11]

[Result] *Three studies are **ongoing** (ISRCTN**339; NCT**361; NCT**314).*

[Conclusion] *Wider publication of **study protocols** would allow a clearer assessment of publication bias.*

e) Dixit 2016 [12]

[Method] *"We also contacted other researchers or nutritional and SCD experts working in this field to identify additional trials (including **unpublished and ongoing** trials)"*

[Result] *"The trial included in the analysis **had no protocol or like resource** outlining previously defined outcomes, therefore, it was difficult to assess for reporting bias."*

Another issue was vagueness reporting of sources, which consequently reduces the transparency of the review. The term *unpublished* in the context of a systematic review alludes to records not written in a scientific journal (e.g. can be written as a poster presentation) but also refers to trial registry records. It was hard to know if the information came from registries, conference abstracts, personal communications with known experts. For example, *"In addition, we identified another 11 studies as **ongoing or completed** but with no data currently available." [13]* Some authors have started to differentiate between TRR or PP as the following example shows "*...there was no indication in any report of **trial registration** on whether a **trial protocol** had been **published** nor did we find any*" [14].

iii) **Guidance algorithm** (Figure 1). As described above, we combined our main sources of data to develop the reporting algorithm.

The aims of the algorithm are to encourage reviewers to report the use of TRR and PP, and help authors improve the reporting of TRR and PP in systematic reviews of interventions. We have focused on systematic reviews of interventions, but this algorithm could also be useful for other types of synthesis work. The algorithm is not a quality assessment instrument to gauge the quality of a systematic review. We use direct excerpts from the systematic reviews (when available) to illustrate findings and guide authors in reporting TRR/PP. If excerpts were not available, we provide a suggestion marked as [example].

The search**:** According to the MECIR standards [15] it is mandatory, in either new or updated systematic reviews, to search for TRR/PP [15]. Boden et al [6] identified guidance regarding the search in major systematic review bodies. Therefore, whether the search yields TRR/PP or not, this information should be reported. If no TRR/PP are foundthis should be documented at minimum in the results section and PRISMA flowchart. For example,

[Example] Results: we found 2 studies, and we found no trial registry records or published protocols that met our eligibility criteria*.*

Screen: Boden et al [6] report a gap (i.e. no guidance) for the selection section of the review (i.e. inclusion/exclusion criteria). If the search identifies TRR/PP**,** the record should be screened and judged as either included or excluded. If excluded at full text, authors should complete the Characteristic of Excluded Studies Table (CES) and add the information to the excluded studies references clearly indicating this was a TRR/PP. For example,

[References-excluded] *"Rohan 2004 Rohan KJ. Cognitive behavioral approaches to seasonal depression [NCT***]. ClinicalTrials.gov [www.clinicaltrials.gov] 2004" [9]*

If the record is included at full text stage, we suggest first to identify the status the study (i.e. ongoing, terminated, completed and unpublished or completed and published), use/follow the standardized terminology, and proceed as follows:

Trial Terminated: full reporting of why a trial ended is important for evidence based decision-making [16]. Terminated clinical trials raise financial, ethical, and scientific concerns. If the trial is terminated for reasons other than results, it is unlikely to introduce bias. On the other hand, if the trial is terminated following results of an interim analysis, biases may be present. This information is essential to evidence synthesis authors. We suggest gathering information from the registry and/or consulting with trial authors directly; following, we suggest presenting the information in the results, discussion, characteristics of included studies, risk of bias or characteristics of excluded studies and references sections as information allows. A few examples are provided below.

[Results] *we found no RCTs in the 2015 update meeting the inclusion criteria for this review. The one RCT identified in the 2014 review as ongoing, which includes children,* ***was terminated*** *(NCT***; characteristic of excluded table). The registry does not contain information on reasons for termination of the trial. We tried contacting the author but after several unsuccessful attempts, the team decided to exclude the study. [17]*

[Results] *Results of the Search: The previously identified ongoing study had been* ***terminated*** *without publication of results and was thus added to the Characteristics of excluded studies table. We identified six new articles for inclusion in the review, and identified that the ongoing study (NCT***) had been closed through poor accrual [18]*

[Results] *Risk of Bias: Incomplete outcome data (attrition bias) Study was* ***prematurely terminated by the sponsor****…. Comments: high risk of attrition bias existed [19]*

Ongoing Trial

Boden et al [6] indicates current guidance suggest identifying ongoing studies for inclusion and to help minimize bias; current guidance suggest describing ongoing studies in the Characteristics of Ongoing Studies table. In addition, current guidance suggest that previously identified ongoing trials should be reviewed for a change of status and/or data. In summary, an ongoing TRR/PP may follow a similar path of an included record. We suggest that reviewers document the presence of ongoing trials in the abstract,

results, PRISMA flowchart, discussion and implications for practice or research. In addition, we support current guidance and suggest ongoing trials should be reported in the Characteristic of Ongoing Studies (COS) table and references. This information could be used as part of decision for next Cochrane update timing.

[Abstract] *Conclusion - It is possible that the findings may change with the inclusion of large* ***ongoing*** *well-organised trials in future updates [20]*

[Conclusion] *Implications for research - The three ongoing GCIG trials will add data to answer the outstanding questions around the optimal IP drug, dose, combination and number of courses of IP chemotherapy. [21]*

Completed and published trials should be included and protocols in this category should be processed as a companion study (i.e. studies associated with each other). Usually companion studies are a pair or a match in characteristics such as author, place, title, outcomes, etc. As current guidance [6] suggest “trial registries can address reporting bias if they provide data on both ongoing and completed trials”. These records should be mentioned in aggregate form in the abstract, and clearly reflect their presence in the results, PRISMA flowchart, discussion, characteristic of included studies table and references.

[Results] *Included studies One study (Jerosch-Herold 2011) had an associated publication, which presented the trial protocol (Jerosch-Herold 2008)[22]*

[References] *Included studies - Kimani 2015{published data only}*
∗Kimani J, Warren CE, Abuya T, Ndwiga C, Mayhew S,Vassall A, et al. Use of HIV counseling and testing and family planning services among postpartum women in Kenya: a multicentre, non-randomised trial. BMC Women'sHealth2015;15:104.
Warren CE, Mayhew SH, Vassall A, Kimani JK, Church K, Obure CD, et al. ***Study protocol*** *for the Integra initiative to assess the benefits and costs of integrating sexual and reproductive health and HIV services in Kenya and Swaziland. BMC Public Health2012;12:973*[23]

Evaluating risk of bias.

[Results] *Risk of Bias. We found the protocol for one RCT (Itani 2010); all of the primary and secondary outcomes pre-specified in the protocol were subsequently reported, and, accordingly, the trial was judged to be at low risk of bias for this domain. We searched, but did not find the protocols for the other included trials, and so the remaining eight RCTs were judged to be at unclear risk of bias [24]*

Completed and unpublished: Conceptual guidance is provided indicating that finding unpublished studies in the review can help minimize bias [6] but there is a gap in the guidance related to its reporting.
A fraction of completed and unpublished trials has data available in the registries. We suggest consulting the trialist to confirm that the available data is accurate and to provide any missing data. Trialists may be working in a draft manuscript or awaiting editorial approval; on the other hand, trialists may have no intention to publish in a scientific journal but they may be willing to share their results. Regardless, the

status (e.g. draft manuscript submitted) and information available for this type of record should be added at least to the results and discussion as appropriate.

[Results] *Effects of the intervention 1.13.1 Clinically significant gamma-glutamyl transpeptidase levels. In this subgroup we only found one relevant trial (n=183) (NCT***). There was a clear difference between asenapine and placebo (RR 3.62....Analysis 1.13) [25]*

[Discussion] *Summary of Main Results We were unable to find full publications for two included studies (NCT*** and NCT***) that were considered to be 'negative trials' by their authors" [25]*

Discussion

A Cochrane systematic review of interventions is an important and detailed document for which clear and thoughtful methodology is established. Well-designed and properly executed systematic reviews of interventions provide the most reliable evidence for healthcare and policy change. We have found inconsistencies in the reporting of trial registry records and published protocols and present an algorithm to guide a more systematic reporting of them. In this study, we recommend an algorithm to help reviewers report use of TRR/PP and to generate discussion.

The algorithm presents a graphical and detailed series of steps for carrying out the reporting of use of TRR/PP in systematic reviews of interventions. As transparency is crucial, we encourage adopting the algorithm so users of the review are able to see where and how the authors have found and use the evidence of interest.

As we noted previously in regard to the available guidance, authors use terminology related to TRR/PP that is confusing and inconsistent in reporting systematic reviews. We recommend employing consistent terminology and citing protocols in the same manner as other document types. We hope this investigation and clarification of key concepts will help to move the field forward. We discourage the use of the word "ongoing" to describe every record found in the trial registries. TRR/PP may be at different stages, and that has consequences for review authors and the evidence included in the systematic review.

Several authors report using the specialized Cochrane groups' trial registers; these registers are developed, maintained, and updated by information specialists. The use of the registers is meant to be a resource to Cochrane group members (teams/authors). Further, to our knowledge, the content of these databases varies across Cochrane groups and the only way we know what is included is to search them individually. The current reporting often presents a ready-made phrase for the Cochrane group that leaves the reader wondering about the inclusion of the trial registries and consequent findings reported in the review. We will discuss this in more detail in a forthcoming publication.

As review authors ourselves, we have experienced first-hand the lack of completeness and up to date information contained in the registries. We are aware that the reporting guide suggested here is to an extent dependent on the completeness of information in the registries. As far as we know, efforts are

currently under way to improve and enforce trialists reporting in registries. We have also experienced the current trend to both register and publish the protocol in a scientific journal, which brings added challenges to current reporting practices. We find our study timely in this regard, as there is an evident need to be transparent about sources and stages of protocols in the systematic reviews. As the practice of protocol registration or publication continues to grow and evolve, our algorithm and conclusions may need to be revised.

We have assumed our readers are familiar with a Cochrane review process and understand the principles behind evidence synthesis. Typically, Cochrane reviews are held to high editorial and methodological standards. Our guidance may help to raise awareness and appeal to a broader systematic review authors audience - in particular those not yet associated with Cochrane practices.

We believe the inquisitive trained review author may have many questions regarding what to do in certain cases presented in the results, for example how to assess the risk of bias of completed and unpublished trial, or how to handle results from a terminated trial. However important issues, these are complicated questions that require further analysis by methodologists.

We encourage review authors to increase their efforts, and time permitting, to seek information from trialists and transparently report the use of protocols in systematic reviews. We, as researchers, owe this effort to those participants who volunteered in the trials, but also to policy makers who trust conclusions of systematic reviews of interventions to undertake impactful policy decisions.

Limitations of this study

By the time of writing this manuscript the Cochrane Handbook (or sections of it) was updated. We are unaware of any new developments planned for the reporting of TRR/PP use. We are aware, however, that new and exciting developments were initiated to ensure both trial registration and reporting of results are available to the scientific community in a timely manner. Newest practices may have an impact on our best practice algorithm which will further need to revise. Last, we are mindful that we have presented a small sample of extracts, representing practices and views of review authors of some Cochrane Editorial Groups to illustrate a point. These practices may not be common practice across the entire community of systematic reviewers in the Cochrane organization. Lastly, methods in evidence synthesis are rapidly evolving; snapshots of practice such as this may need to be updated in the near future.

Conclusions

Our study expands on available guidance to describe in greater detail the reporting of registry records and published protocols for review authors. We presented an algorithm for review authors use and reporting of protocols, a timely investigation in an era were evidence synthesis informs health and health care decisions. We hope the algorithm will help bring transparency in the reporting of protocols in systematic reviews, bring clarification to current fuzziness in terminology and reporting, and ultimately lead to higher quality systematic reviews. We invite researchers to provide feedback on our work for its improvement

and dissemination. Last, we look forward to further discussions on the use of trial protocols in systematic reviews of interventions.

Abbreviations

CES: Characteristic of Excluded Studies Table

COIS: Characteristics of Included Studies Table

MECIR: Methodological Expectations for Cochrane Intervention Reviews

RCT: randomized control trial

RoB: Risk of Bias

SR: systematic review

Declarations

Ethics approval and consent to participate: not applicable

Consent for publication: not applicable

Availability of data and material: The data extracted and/or analysed from the 169 Cochrane Reviews during the current study are not publicly available but can be available from the corresponding author on reasonable request.

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Authors' contributions: JB and CB conceived the idea of this paper. CB conducted the search; JB, JME and CB extracted data, JB conducted data analysis and drafted the first manuscript. JME, AJB contributed to the writing of the manuscript. AJB contributed content and methodological expertise. All authors read and approved the final manuscript.

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References

1. Chan A-W: Out of sight but not out of mind: how to search for unpublished clinical trial evidence. *BMJ* 2012, 344:d8013.
2. Chandler J HJ, Deeks JJ, Davenport C, Clarke MJ. : Introduction. In: *Cochrane Handbook for Systematic Reviews of Interventions Version 520.* Edited by Higgins JPT CR, Chandler J, Cumpston MS: Cochrane Community; 2017: 3/50.
3. Reveiz L, Chan A-W, Krleža-Jerić K, Granados CE, Pinart M, Etxeandia I, Rada D, Martinez M, Bonfill X, Cardona AF: Reporting of Methodologic Information on Trial Registries for Quality Assessment: A Study of Trial Records Retrieved from the WHO Search Portal. *PLOS ONE* 2010, 5(8):e12484.
4. Publishing and Editorial Issues. Clinical Trials [http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html]
5. Elliott JH, Synnot A, Turner T, Simmonds M, Akl EA, McDonald S, Salanti G, Meerpohl J, MacLehose H, Hilton J *et al*: Living systematic review: 1. Introduction—the why, what, when, and how. *Journal of Clinical Epidemiology* 2017, 91:23-30.
6. Boden C, Bidonde J, Busch A: Gaps exist in the current guidance on the use of randomized controlled trial study protocols in systematic reviews. *Journal of Clinical Epidemiology* 2017, 85:59-69.
7. Wallace BC, Small K, Brodley C, Lau J, Trikalinos TA: Deploying an interactive machine learning system in an evidence-based practice center: abstrackr. In. ACM International Health Informatics Symposium (IHI) 2012: 819-824.
8. Bruschettini M, Romantsik O, Zappettini S, Banzi R, Ramenghi LA, Calevo MG: Antithrombin for the prevention of intraventricular hemorrhage in very preterm infants. *Cochrane Database of Systematic Reviews* 2016(3).
9. Forneris CA, Nussbaumer B, Kaminski-Hartenthaler A, Morgan LC, Gaynes BN, Sonis JH, Greenblatt A, Wipplinger J, Lux LJ, Winkler D *et al*: Psychological therapies for preventing seasonal affective disorder. *Cochrane Database of Systematic Reviews* 2015(11).
10. Corbetta D, Sirtori V, Castellini G, Moja L, Gatti R: Constraint-induced movement therapy for upper extremities in people with stroke. *Cochrane Database of Systematic Reviews* 2015(10).
11. Baker PRA, Francis DP, Hairi NN, Othman S, Choo WY: Interventions for preventing abuse in the elderly. *Cochrane Database of Systematic Reviews* 2016(8).
12. Dixit R, Nettem S, Madan SS, Soe HHK, Abas ABL, Vance LD, Stover PJ: Folate supplementation in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2016 (3).
13. Day AC, Gore DM, Bunce C, Evans JR: Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery. *Cochrane Database of Systematic Reviews* 2016(7).

14. McNamara HC, Crowther CA, Brown J: Different treatment regimens of magnesium sulphate for tocolysis in women in preterm labour. *Cochrane Database of Systematic Reviews* 2015(12).
15. Methodological Expectations of Cochrane Intervention Reviews
16. Transparent Reporting of Trials [http://www.consort-statement.org/]
17. Farne HA, Cates CJ: Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015(10).
18. Phillips RS, Friend AJ, Gibson F, Houghton E, Gopaul S, Craig JV, Pizer B: Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. *Cochrane Database of Systematic Reviews* 2016(2).
19. He D, Zhang C, Zhao X, Zhang Y, Dai Q, Li Y, Chu L: Teriflunomide for multiple sclerosis. *Cochrane Database of Systematic Reviews* 2016(3).
20. Smith SM, Wallace E, O'Dowd T, Fortin M: Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database of Systematic Reviews* 2016(3).
21. Jaaback K, Johnson N, Lawrie TA: Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database of Systematic Reviews* 2016(1).
22. Rodrigues JN, Becker GW, Ball C, Zhang W, Giele H, Hobby J, Pratt AL, Davis T: Surgery for Dupuytren's contracture of the fingers. *Cochrane Database of Systematic Reviews* 2015(12).
23. Lopez LM, Grey TW, Chen M, Denison J, Stuart G: Behavioral interventions for improving contraceptive use among women living with HIV. *Cochrane Database of Systematic Reviews* 2016(8).
24. Yue J, Dong BR, Yang M, Chen X, Wu T, Liu GJ: Linezolid versus vancomycin for skin and soft tissue infections. *Cochrane Database of Systematic Reviews* 2016(1).
25. Hay A, Byers A, Sereno M, Basra MK, Dutta S: Asenapine versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews* 2015(11).
26. Conn VS, Valentine JC, Cooper HM, Rantz MJ: Grey literature in meta-analyses. *Nursing research* 2003, 52(4):256-261.
27. Viergever RF, Karam G, Reis A, Ghersi D: The quality of registration of clinical trials: still a problem. *PLoS One* 2014, 9(1):e84727.
28. Dwan K, Gamble C, Williamson PR, Kirkham JJ: Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review. *PLoS One* 2013, 8(7):e66844.
29. Moreno SG, Sutton AJ, Turner EH, Abrams KR, Cooper NJ, Palmer TM, Ades AE: Novel methods to deal with publication biases: secondary analysis of antidepressant trials in the FDA trial registry database and related journal publications. *Bmj* 2009, 339:b2981.
30. Dubben H-H: New methods to deal with publication bias. *BMJ* 2009, 339:b3272.
31. Farquhar CM, Showell MG, Showell EAE, Beetham P, Baak N, Mourad S, Jordan VMB: Clinical trial registration was not an indicator for low risk of bias. *J Clin Epidemiol* 2017, 84:47-53.

32. Roberts J: Trial Registration, Transparency, and Selective Reporting: Let's Get Clear About What Is Needed in Headache Medicine. *Headache* 2016, 56(1):3-7.
33. Mann E, Nguyen N, Fleischer S, Meyer G: Compliance with trial registration in five core journals of clinical geriatrics: a survey of original publications on randomised controlled trials from 2008 to 2012. *Age and ageing* 2014, 43(6):872-876.
34. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, Williamson PR: The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010, 340.
35. Dwan K, Gamble C, Williamson PR, Altman DG: Reporting of clinical trials: a review of research funders' guidelines. *Trials* 2008, 9:66.
36. Pearson M, Peters J: Outcome reporting bias in evaluations of public health interventions: evidence of impact and the potential role of a study register. *Journal of epidemiology and community health* 2012, 66(4):286-289.
37. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG: Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *Jama* 2004, 291(20):2457-2465.
38. Hahn S, Williamson PR, Hutton JL: Investigation of within-study selective reporting in clinical research: follow-up of applications submitted to a local research ethics committee. *Journal of Evaluation in Clinical Practice* 2002, 8(3):353-359.
39. Li G, Abbade LPF, Nwosu I, Jin Y, Leenus A, Maaz M, Wang M, Bhatt M, Zielinski L, Sanger N *et al*: A systematic review of comparisons between protocols or registrations and full reports in primary biomedical research. *BMC medical research methodology* 2018, 18(1):9.

Box 1

Box 1

Trial protocol: is the plan or set of steps to be followed when conducting a study. A trial protocol often contains the rational for the study, objective(s), and the methods that will be used to locate, select, and collect information from participants. It contains statistical considerations and organization of a trial, and ensures the safety of the trial subjects and integrity of the data collected.

Completed and un/published trial: a completed trial is one that has finished data collection, completed the statistical analysis and reached conclusions based on the analysis. After that authors may choose to write up and published the trial in a journal/report format or not (unpublished). Not all trials registered aim for publication; some are conducted with the pure aim of experimentation, and therefore results are never published.

Published protocol (PP): a trial protocol that is published in a journal often available to the public. Similar to the trial protocol, often includes a description of the objectives, design methodology, statistical considerations and organization of the trial in addition to journal requests. Published protocols create the expectation of a future publication, are static records, and no follow up is provided or updated by the journal. The only way to know the status of the trial (recruiting, terminated, etc.) is by contacting the authors.

Trial registry: is an official platform for registering a trial or study including human subjects. To date, trial registration is not mandatory but strongly encouraged. Some journal policies such as manuscript acceptance upon proof of prospective trial registration has helped increase the number of registrations. For Cochrane authors, search of ClincalTrial.gov and WHO portal are mandatory MECIR standards.

Trial registry record (TRR): is the publication of an internationally agreed set of information about the design, conduct and administration of clinical trials. These details are published on a publicly-accessible website managed by a registry (WHO)

Ongoing trial: means the trial is active and being conducted at the time and either locating, recruiting, collecting data, or analysing and preparing the manuscript.

MECIR (Methodological Expectations for Cochrane Intervention Reviews) are standards for conduct and reporting. MECIR standards cove mandatory and non-mandatory items. Trial registry search is a mandatory MECIR standard for Cochrane authors. .

Figures

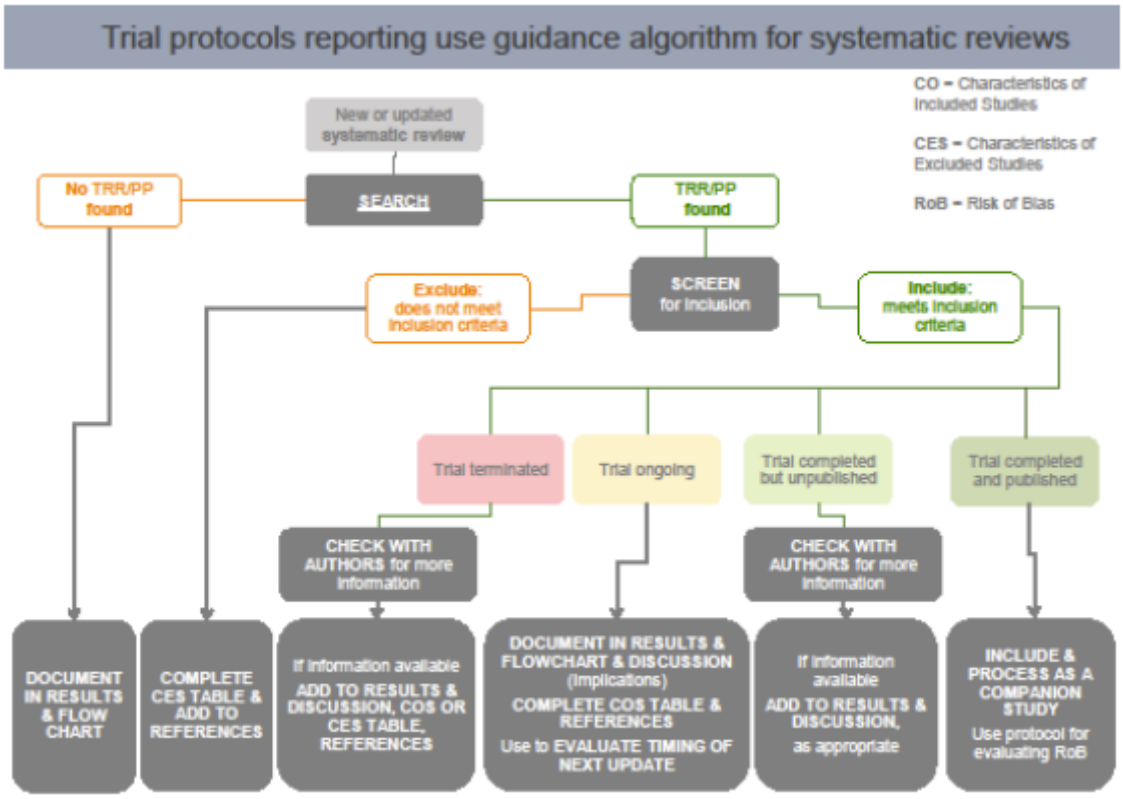

Figure 1

Trial protocols reporting use guidance algorithm

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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